

Some Substitution Reactions of 4-(2'-Thienyl)pyrazoles and
4-(3'-Thienyl)pyrazoles

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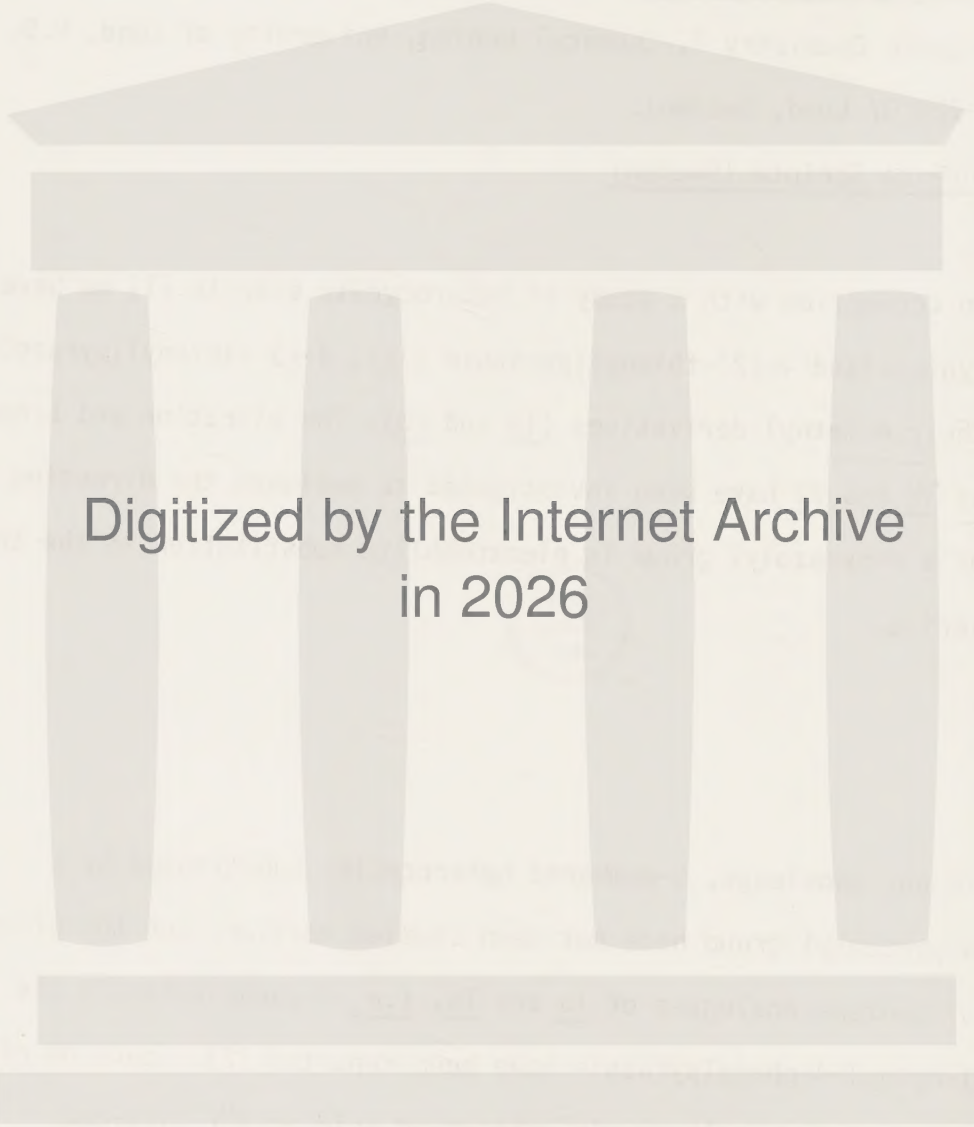
Abstract

Some substitution reactions of 4-(2'-thienyl)pyrazoles and 4-(3'-thienyl)pyrazoles. Liljefors, S.; Gronowitz, S. (Division of Organic Chemistry 1, Chemical Center, University of Lund, P.O. Box 740, S-220 07 Lund, Sweden).

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In connection with a study of heterocyclic biaryls [1] we have synthesized 4-(2'-thienyl)pyrazole (1a), 4-(3'-thienyl)pyrazole (2a) and their N-methyl derivatives (1b and 2b). The nitration and bromination of 1b and 2b have been investigated to evaluate the directing effect of a 4-pyrazolyl group in electrophilic substitution in the thiophene series.

To our knowledge, 5-membered heterocycles substituted by a 4-pyrazolyl group have not been studied earlier, but the nitration of benzene analogues of 1a and 1b, i.e. 4-phenylpyrazole and 1-methyl-4-phenylpyrazole have been reported [2]. Reaction of 1-methyl-4-phenylpyrazole with mixed acid at 0°C afforded 4-(o,p-dinitrophenyl)pyrazole. In contrast to this easy dinitration, the nitration of 4-phenylpyrazole under similar conditions failed, while nitration of 1-methyl-4-(p-tolyl)pyrazole with nitric acid gave only 1-methyl-3-nitro-4-(p-tolyl)pyrazole.



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When 1-methyl-4-phenylpyrazole was treated with a large excess of acetyl nitrate in acetic acid, complex mixtures of mono- and dinitro isomers were obtained. The 3-position of the pyrazole ring and the o-position of the phenyl substituent had similar reactivity, both being nitrated more rapidly than the p-position.

Synthesis of 1 and 2

For the synthesis of 1 and 2 three routes were tested (Scheme 1). The first one was based on the fact that 2-thienylcopper (3), prepared from 2-thienyllithium and copper(I) bromide or copper(I) iodide in ether, can be reacted with a number of iodo arenes in pyridine or quinoline to give the corresponding 2-arylthiophenes in reasonable yields [3]. It was also known that 4-iodo-1-methylpyrazole (4b) in refluxing pyridine undergoes a copper-promoted coupling with terminal acetylenes to give 4-ethynylpyrazoles [4]. Reaction of 4b with a 3-fold excess of 3 in refluxing pyridine gave 33 % of 1b. 4-Iodopyrazole (4a) could also be used in this reaction, although the yield of 1a was lower.

This route could not possibly be used for the synthesis of 2 as 3-thienyllithium - a conceivable precursor of the unknown 3-thienylcopper - rearranges [5] to 2-thienyllithium under the conditions used to prepare 2-thienylcopper. For the synthesis of 2 we therefore wanted to try the reversed coupling mode: 4-pyrazolyl-copper + 3-iodothiophene. However, preliminary attempts to react 1-methyl-4-pyrazolyl-lithium - prepared from 1-methyl-4-bromopyrazole and butyllithium [6] - with copper(I) bromide or copper(I) iodide

in ether did not give any evidence of the formation of a corresponding pyrazolyl copper.

Vinamidinium salts [7] like 5 are highly electrophilic 1,3-dicarbonyl equivalents and it was thought that they could be used as precursors for pyrazoles [8]. Thus, in route 2, 1-dimethyl-3-dimethyl-immonio-2-(5-chloro-2-thienyl)propen-1 perchlorate (5) [9] was reacted with hydrazine hydrate in refluxing methanol to give 4-(5'-chloro-2'-thienyl)pyrazole (6) in 66 % yield. Attempts to dechlorinate 6 with copper in refluxing propionic acid [10] - which readily dechlorinates for example 5-(5'-chloro-2'-thienyl)pyrimidine [9] - led to recovery of starting material. Also, dechlorination with magnesium in isopropanol/decaline [11] or lithium in 1-butanol/tetrahydrofuran [12] failed. Further trials on dechlorination of 5 were abandoned as we at this stage found that thienylmalonaldehydonitriles could be hydrogenated in the presence of Raney-nickel to the thienylaminopropenals (7a) and (7b) [9], which yielded 1a and 2a on reaction with hydrazine hydrate (Route 3). Later, however, we have discovered that 6 can be conveniently dechlorinated by the action of 3 equivalents of butyllithium in THF at 0°C.

The N-methyl derivatives (1b) and (2b) were obtained by the action of methyl iodide in THF on the anions of 1a and 2a, respectively - prepared in situ using sodium hydride as base.

Compounds 1b and 2b could be further alkylated with dimethyl sulfate in refluxing THF and the corresponding 1,2-dimethyl-4-(2'- or 3'-thienyl)pyrazolium ions were isolated as perchlorates 1c and 2c.

Reactions

Compounds 1a, 1b, 2a and 2b all react readily with 98 % sulfuric acid. After 20 min. reaction at 0°C the recovery of starting material in all cases was in the range of 5-10 %. Probably, sulfonation occurs as the reaction mixture after quenching on ice gave clear, colourless solutions, which after neutralization and ether extraction only yielded starting material as above.

For comparison, 1-(2'-thienyl)pyrazole [1] was reacted with sulfuric acid under identical conditions and in this case the recovery of starting material was higher (59 %).

The products from preliminary nitrations and brominations of 1a and 2a could not be properly analysed by GLC due to excessive tailing or too low volatility. Further, the use of NMR as an analytical tool was obstructed by the low solubility of some of the compounds. These difficulties were circumvented by using the N-methyl derivatives 1b and 2b as substrates for nitration and bromination.

Nitration of 1b and 2b were performed with three different reagents: nitric acid in trifluoroacetic acid (TFA), nitric acid in sulfuric acid and acetyl nitrate in acetic anhydride. Brominations were made with N-bromosuccinimide in acetic acid. The results of these reactions are summarized in Table I. The structures of the products were determined by MS and NMR. The quantitative analyses of the mixtures obtained were performed by GLC and/or by integration of the NMR spectra of the crude products.

Nitrations in TFA (entries 1 and 7) yielded mononitro products in good yield. Compound 1b gave a 1:2 mixture of 1-methyl-4-(3'-nitro-2'-thienyl)pyrazole (8) and 1-methyl-4-(5'-nitro-2'-thienyl)pyrazole (10). The assignments of 8 and 10 were based on the presence in the ^1H NMR spectra of thiophene doublets with coupling constants of 5.9 and 4.4 Hz, respectively.

Compound 2b gave 1-methyl-4-(2'-nitro-3'-thienyl)pyrazole (14), $J_{4',5'} = 5.8$ Hz, as the major product but small amounts of 1-methyl-4-(5'-nitro-3'-thienyl)pyrazole (16), $J_{2',4'} = 1.7$ Hz, could also be isolated. According to GLC/MS, the crude product also contained 1 % of 1-methyl-4-(4'-nitro-3'-thienyl)pyrazole (15). (For discussion of the structure of 15, see below.)

The nitrations in sulfuric acid gave mixtures of mono- and dinitro compounds when 1.0 equivalent of nitric acid was used (entries 2 and 8). A probable reason for this is that the substrate is partially consumed by sulfonation before nitration occurs. Different ways of mixing substrate, sulfuric and nitric acids or the use of dichloromethane as co-solvent [13] did not alter the situation. However, by using a deficiency of nitric acid (0.5 equivalent), the dinitration was suppressed. In these latter experiments, the reaction mixtures were kept at room temperature for half an hour before quenching. Unconsumed starting material was thereby probably sulfonated and dissolved in the aqueous phase on work-up, as only traces of starting material could be detected in the crude products isolated. It was checked that the nitro products were not sulfonated to any considerable extent under the conditions used in these experiments.

Nitration (0.5 eq. of HNO_3) of 1b (entry 3) gives mainly 8 (20 %) and 10 (69 %), i.e. the isomer distribution obtained is similar to that observed by nitration in TFA. GLC/MS indicates formation also of a small amount (< 1 %) of another mononitro isomer, 9, (m/e 209, fragmentation of 0, NO and NO_2 from molecular ion). No attempts were made to isolate 9, but tentatively its structure is supposed to be 1-methyl-4-(4'-nitrothienyl)pyrazole. The use of two equivalents of nitric acid (entry 4) led to a high yield of one dinitro compound. This must have both 8 and 10 as precursors and consequently its structure is 1-methyl-4-(3',5'-dinitrothienyl)pyrazole (11).

Nitration (0.5 eq. of HNO_3) of 2b in sulfuric acid (entry 9) gave 14 and 16 in a 1:1 ratio together with a minor amount of 15. Compound 15 has not been isolated, but GLC/MS data ($M^+ = 209$ m/e and fragmentation typical for a nitro group) give evidence for a mononitro isomer structure. When one equivalent of nitric acid was used (entry 8), only traces of 15 could be detected in the product, but instead two dinitro compounds, 17 and 18, had been formed. Presumably, 15 has been consumed in a second nitration step (15 is not sulfonated under the conditions used). Two equivalents of nitric acid gave a mixture of 17 and 18 in a high yield. Both 17 and 18 have ^1H NMR spectra with three singlets in the aromatic region. In both cases, two of these singlets are slightly broadened and may thus be attributed to two pyrazole hydrogens [14]. Both compounds have obviously both nitro groups bound to the thiophene ring. Through ^{13}C NMR it was shown that

17 [$J(\text{C5}, \text{H5}) = 199 \text{ Hz}$] is the 2',4'-dinitro derivative, while 18 [$J(\text{CH4}', \text{H4}') = 182 \text{ Hz}$] is the 2',5'-dinitro derivative [15].

To check if the assumption that 15 acts as a precursor to a dinitro derivative is consistent with the results obtained in entries 8 and 9, the 2'-nitro derivative 14 was nitrated in sulfuric acid (entry 11). This experiment gave 17 and 18 in a ratio of 79:21. This means that the decrease of 14 of 13 mol % (when comparing entries 9 and 8) should lead to an amount of 17 of 10 % (compared to 14 % of 17 in entry 8). It thus seems reasonable to assume that the remaining 4 % of 17 in entry 8 has been formed via 15. Compound 15 then must be the 4'-nitrothienyl derivative.

Nitration with acetyl nitrate gave in the case of 1b (entry 5) mainly a 2:3 mixture of 8 and 10, while the major product from 2b was 14 (entry 12). In both cases, however, minor amounts of a new mononitro isomer, 12 and 19, respectively, were indicated by GLC/MS. Compounds 12 and 19 both are less polar than the other mononitro isomers in this study, reflected in significantly shorter retention times in GLC (and higher R_f values in TLC).

Compound 19 has been isolated and its NMR spectrum shows that the nitro group is bound to the pyrazole ring but to which position is uncertain.

As 1-methyl-4-phenyl-pyrazole on nitration with acetyl nitrate gives the 3-nitropyrazole derivative [2], it is tempting to propose an analogous structure for 19. However, such a suggestion is contradicted by some spectroscopic data of 19. Comparing the ^1H NMR spectra of 2b and 19 shows that the N-methyl signal is shifted 0.34 ppm (CDCl_3) or 0.33 ppm (DMSO-d_6) downfield when the nitro group is introduced. A comparison with the literature shows that a nitro group

in the 3-position of some 1-methyl-4-R-pyrazoles gives a corresponding shift of the N-methyl signal of 0.15 (R = H, CDCl_3) [16], 0.17 (R = 2,4-dinitrophenyl, DMSO-d_6) and 0.15 ppm (R = 2,4,6-trinitrophenyl, DMSO-d_6) [17] downfield. When the nitro group instead is introduced in the 5-position of the pyrazole, it is nearer to the methyl group and the shifts are larger: 0.37 (R = H, CDCl_3) and 0.34 ppm (R = 2,4-dinitrophenyl, DMSO-d_6) downfield.

The MS of 19 shows fragment ions of M-17 (OH) and M-29 (CH_3N). This type of fragmentation is shown by 1-methyl-5-nitropyrazole but not by 1-methyl-3-nitropyrazole [16].

From these data it seems reasonable to assume that 19 is the 5-nitro derivative.

From the similarity between 12 and 19 with respect to the conditions of their formation, chromatographic properties and MS, also 12 is assumed to be a 5-nitropyrazole.

Nitrations of the pyrazolium ions 1c and 2c with nitric acid in TFA are complete within 15 min. at 25°C . The NMR spectra of the reaction solutions showed that nitration of 1c occurred in the 3'- and the 5'-positions in a ratio of 3:7, while 2c was nitrated in the 2'- and 5'-positions in a ratio of 7:3.

Compounds 1c and 2c are also readily sulfonated. For example, a sample of 1c was dissolved in 98 % sulfuric acid at 0°C and after 20 min. at this temperature, the NMR spectrum was recorded. According to this, sulfonation was almost complete, occurring in the 3'- and 5'-positions in a ratio of 1:3.

Bromination of 1b and 2b with NBS in acetic acid (entries 6 and 13) are rapid processes, the reactions being complete in less than one minute. Compound 1b gives selectively and in high yield 1-methyl-4-(5'-bromo-2'-thienyl)pyrazole (13), $J(H3',H4') = 3.9$ Hz. Compound 2b gives 1-methyl-4-(2'-bromo-3'-thienyl)pyrazole (20), $J(H4',H5') = 5.8$ Hz, contaminated with a small amount of another monobromo isomer (21) (GLC/MS gives $M^+ = 244, 242$ m/e, 100 %).

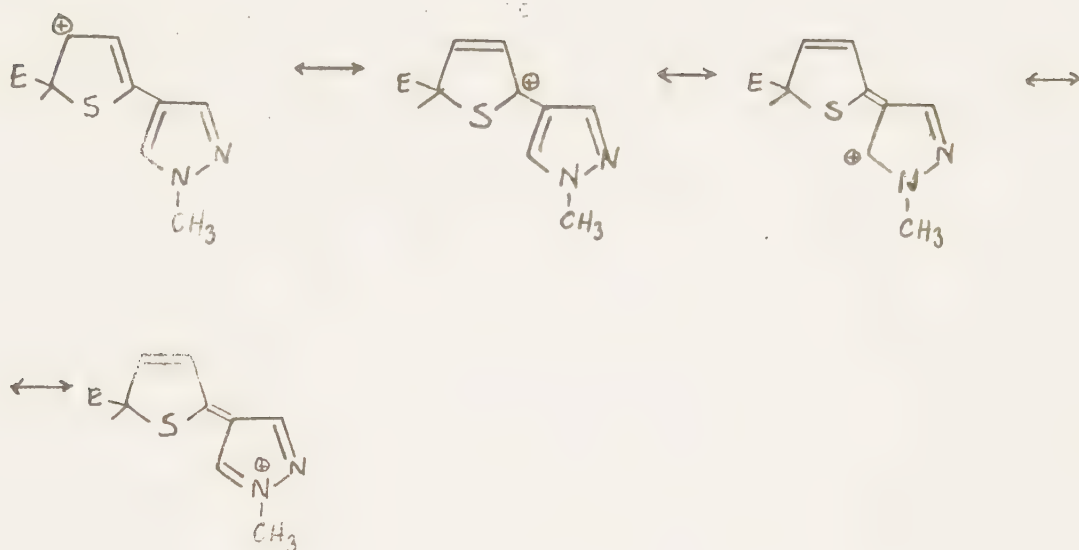
Compound 21 has not been isolated but its structure can be deduced from the MS.

In the MS from all 3'- or 5'-substituted derivatives of 1b and all 2'- or 5'-substituted derivatives of 2b in this study, m/e = 119 is a fragment ion of high (or highest) intensity [18]. On the other hand, when the substituent is bound to the pyrazole part of 1b or 2b, m/e = 119 is of low importance. In the MS of 21, m/e = 119 is the peak of highest intensity (54 %) next to M^+ . From these facts, 21 is suggested to have its bromine in the 2'-position.

Discussion

For the 1-(thienyl)pyrazoles we have shown that the 1-pyrazolyl group activates the thiophene ring towards electrophilic substitution [1]. This is obviously also true for the 1-methyl-4-pyrazolyl group, evidence for which being for example the rapid NBS bromination of 1b and 2b. NBS bromination of thiophene under the conditions used for 1b and 2b calls for a reaction time of several hours [1]. In terms of the resonance theory, these results indicate that the σ -complexes following an attack of an electrophile in the 5'- (or 3'-) position of

1b or the 2'-position of 2b are stabilized by a +M effect of the pyrazole moiety.



It is noteworthy that two different resonance structures contributing to the +M effect can be written for the 4-pyrazolyl group, but only one for the 1-pyrazolyl group. For that reason one could perhaps expect a greater activation from the 4-pyrazolyl group than from the 1-pyrazolyl. A comparison of data for NBS-bromination of 2b (reaction complete after 1 min. at 25°C) with the same reaction for the corresponding 1-pyrazolyl compound, i.e. 1-(3-thienyl)pyrazole (not complete after 4 min. at 25°C) [1] gives an indication of this difference in activation.

To get more data for such a comparison, a competitive experiment was made between equimolar amounts of 1b and 1-(2-thienyl)pyrazole, which were reacted with 0.1 equivalent of NBS (based on total amount of thiophenes) in acetic acid at 25°C. Compound 13 and 1-(5-bromo-2-thienyl)pyrazole were formed in a ratio of 5.4:1.

Also in strongly acidic medium the 4-pyrazolyl thiophenes are more reactive than the 1-pyrazolyl analogues. This is shown by the easy dinitration and in the more rapid sulfonation of 1a, 1b, 2a and 2b compared to 1-(2'-thienyl)pyrazole. Protonation of a pyrazolyl group at N2 of course must diminish its +M effect and the reason for the higher reactivity of the 4-pyrazolylthiophenes may be that these compounds even in sulfuric acid react in an unprotonated state, while the 1-pyrazolylthiophenes -which is most likely [1] - react protonated. However, the assumption that the 4-pyrazolylthiophenes should be sulfonated as unprotonated species is not very reasonable in view of the results from sulfonation of 1b ($\approx 90\%$ sulfonation after 20 min. at 0°C) and 1c (isoelectronic with protonated 1b, sulfonation almost complete after 20 min. at 0°C). If sulfonation, which is ranked among the more selective electrophilic substitutions [19], occurs on what must be the majority species, i.e. the protonated 4-thienylpyrazoles, the less selective nitration in sulfuric acid also must occur on the same type of substrate.

A more plausible explanation for the higher reactivity also in strong acid of the 4-pyrazolylthiophenes is that the 4-pyrazolium group does not deactivate the thiophene nucleus as much as the 1-pyrazolium group.

In the case of the 4-pyrazolium thiophenes, the positive pole is further from the reactive centres in the thiophene ring than for the 1-pyrazolium compounds, i.e. inductive and field effects can be expected to be more pronounced in the latter case, thus contributing to the lower reactivity of the 1-pyrazolium compounds.

Also mesomeric effects may influence this difference in reactivity. Considering the possibility that the appropriate σ -complexes may be stabilized by +M effects from the pyrazolium parts, a study of the resonance hybrids shows that for the 4-pyrazolium group three structures can be written but for the 1-pyrazolium group only one without charged neighbour atoms.

Argument for a +M effect from the 4-pyrazolium group is given by the clear ortho-para pattern obtained by nitration of 1b in sulfuric acid (cf. entry 3) and by nitration of 1c in TFA (3'- and 5'-nitration in ratio 3:7). Also the corresponding nitrations of 2b (cf. entry 9) and 2c (2'- and 5'-nitration in ratio 7:3) with their comparatively large amount of 2'-substitution give support for this argument.

Experimental

Melting points are uncorrected. The ^1H NMR spectra were recorded with Varian A60, Jeol PMR-60 or Jeol MH-100 spectrometers. ^{13}C NMR spectra were recorded with a Jeol FX-60 NMR spectrometer. The shifts were determined from proton decoupled spectra with TMS as internal standard. The MS were recorded on an LKB A 9000 spectrometer. GLC analyses were carried out on a Varian aerograph 1400 gas chromatograph equipped with a flame ionization detector.

Pyrazole [20], 1-methylpyrazole [6] and 100 % nitric acid [21] were prepared according to methods described in the literature.

4-Iodopyrazole (4a). When used on 0.1 mol scale, the literature method (5 mmol) [22] called for long reaction time (30 h) and the high yield could not be reproduced. In hydrogen phosphate buffer [23] the reaction is faster and excess iodine is not necessary.

A solution of iodine (127 g, 0.50 mol) and sodium iodide (125 g, 0.83 mol) was dropped into a solution of pyrazole (34.0 g, 0.50 mol) and sodium monohydrogen phosphate dihydrate ($\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$, 178 g, 1.00 mol) in water (400 ml) at 90-100 °C. The mixture was gently refluxed for 2 h. and was then decolourized with some sodium hydrogen sulfite. After cooling, ether (150 ml) was added with stirring. When no solid remained, the ether phase was separated and the water phase extracted with ether. The combined ether phases were washed (H_2O), dried (MgSO_4), filtered through neutral alumina and evaporated. The residue was recrystallized from cyclohexane and 84.9 g (87 %) of 4-iodopyrazole was obtained as white needles, m.p. 109-110 °C. Lit. [22] 108.5 °C, [23] 112 °C.

1-Methyl-4-iodopyrazole (4b) has been prepared by iodination of 1-methylpyrazole with potassium triiodide [22] or iodine/iodic acid [4]. The following procedure in the three steps tetramethoxypropane → pyrazole [20] → 4-iodopyrazole → 1-methyl-4-iodopyrazole gives higher yield with less work.

Conc. hydrochloric acid (42 ml, 0.50 mol) was cautiously dropped into a cooled (external ice bath) solution of hydrazine hydrate (12.5 g, 0.250 mol) in methanol (25 ml). When the addition was complete, 1,1,3,3-tetramethoxypropane (41.0 g, 0.250 mol) was added and the mixture was heated on a water bath for 1 h., whereafter the methanol was distilled off until the distillation temperature reached 99 °C.

To the residue water (100 ml), sodium phosphate ($\text{Na}_3\text{PO}_4 \cdot 12\text{H}_2\text{O}$, 190 g, 0.50 mol) and a solution of iodine (63.5 g, 0.250 mol) and sodium iodide (62.5 g) in water (50 ml) were added and the mixture was refluxed for 2 h. Excess iodine was destroyed by addition of sodium hydrogen sulfite and after cooling the mixture was extracted with ether. The combined extracts were evaporated which yielded 43.6 g of crude 4-iodopyrazole (not suitable for preparation of pure 4-iodopyrazole). The crude product (0.225 mol) was dissolved in 2 M aq. NaOH (225 ml) and dimethyl sulfate (56.8 g, 0.45 mol, 43 ml) was rapidly dropped into the resulting solution with stirring and external cooling (water bath at 25 °C). After reaction for 15 min. at 25 °C, the mixture was stirred at 95-100 °C for 1 h. After cooling, the mixture was extracted with ether. The combined extracts were washed (H_2O), dried (MgSO_4), filtered through silica and evaporated. The residual solid (42.2 g) was distilled through an apparatus suitable for distillation of crystallizing solids, which yielded 38.8 g (74 % based on tetramethoxypropane) of 1-methyl-4-iodopyrazole, b.p. 105-106 °C/2 kPa, m.p. 62-63 °C. Recrystallization from hexane (120 ml) gave 35.4 g of white prisms, m.p. 63-64 °C. Lit.: 64-65 °C [22] and 62-63 °C [4].

1-Methyl-4-bromopyrazole has been prepared by adding a fourfold excess of bromine to 1-methylpyrazole in chloroform [24]. More convenient is the use of an equimolar amount of bromine in aqueous acetate buffer, which is utilized in the following one-pot procedure starting from tetramethoxypropane → pyrazole → 1-methylpyrazole → 1-methyl-4-bromopyrazole.

An acidic water solution of pyrazole (0.25 mol) was prepared as described in the synthesis of 4b. When the methanol had been distilled off, the reaction mixture was cooled and a solution of sodium hydroxide (40 g, 1.0 mol) in water (250 ml) was added. After cooling to room

temperature, dimethyl sulfate (63.1 g, 0.50 mol, 47.5 ml) was rapidly dropped into the efficiently stirred solution. The mixture was stirred at ambient temperature for 15 min. and was then heated on a water bath (100 °C) for 1 h.

After cooling, acetic acid was added to pH $\approx$ 7, followed by sodium acetate (34 g, 0.25 mol). A solution of bromine (40.0 g, 0.25 mol, 12.8 ml) in acetic acid (25 ml) was added dropwise with stirring until the colour of bromine in the reaction mixture was permanent.

After addition of some sodium hydrogen sulfite, the mixture was made alkaline with conc. aqueous ammonia. The heavy oil was separated and the water phase extracted with ether. The combined organic phases were washed (H₂O), dried (MgSO₄) and evaporated. The residual oil was distilled which gave 25.0 g (62 %, based on tetramethoxypropane) of 1-methyl-4-bromopyrazole as a colourless liquid, b.p. 68-70 °C/1.6 kP_a, $n_D^{20} = 1.5298$. Lit.: 76-78 °C/2.4 kP_a [24].

1-Methyl-4-(2'-thienyl)pyrazole (1b) from 2-thienyl copper.

1-Methyl-4-iodopyrazole (4b) (4.16 g, 20 mmol) was reacted with 2-thienyl copper (60 mmol) in dry pyridine (150 ml) according to the general procedure of Nilsson and Ullenius [3]. After 13 h. at 110-115 °C, all 4b was consumed and work-up yielded after two recrystallizations from methanol/water 1.1 g (33 %) of 1b as white plates, m.p. 64-65 °C. [Found: C 58.5; H 5.0; N 17.2; S 19.6. Calc. for C₈H₆N₂S (164.2): C 58.5; H 4.91; N 17.06; S 19.53.] NMR (100 MHz, CDCl₃): δ 7.65 (H3 or H5, s, 1H), 7.50 (H3 or H5, s, 1H), 7.25-6.93 (H3', H4' and H5', m, 3H), 3.88 (CH₃, s, 3H). m/e (%): 164 (100, M⁺), 163 (6), 149 (3), 137 (3), 136 (7), 123 (12), 122 (14), 119 (5).

4-(2'-Thienyl)pyrazole (1a) from 2-thienyl copper. Starting from 4-iodopyrazole (4a) (3.88 g, 20 mmol), the reaction above was performed at 110-115 °C for 20 h. Work-up afforded after sublimation (140 °C/25 P_a) 0.66 g (22 %) of 1a as white crystals, m.p. 164-165 °C. [Found: C 55.9; H 4.10; N 18.9; S 21.3. Calc. for C₇H₆N₂S (150.2): C 55.97; H 4.03; N 18.65; S 21.35.] ¹H NMR (60 MHz, acetone-d₆): δ 7.89 (H3 and H5, s, 2H), 7.26-7.01 (H3', H4' and H5', m, 3H). m/e (%): 150 (100, M⁺), 149 (6), 123 (9, M-HCN), 122 (9), 105 (9, M⁺-CHS), 96 (27, M⁺-2HCN).

4-(5'-Chloro-2'-thienyl)pyrazole (6). Hydrazine hydrate (3.00 g, 60 mmol) was added to a refluxing solution of 1-dimethyl-3-dimethyl-imonio-2-(5-chloro-2-thienyl)propen-1 perchlorate (13.73 g, 40 mmol) in methanol (100 ml). The mixture was refluxed for 1 h. and was then treated with charcoal and filtered hot. Hot water was added to the hot filtrate until precipitation started. After cooling, the precipitate was filtered off and recrystallized from methanol/water giving 4.90 g (66 %) of the title compound as slightly yellow plates, m.p. 174-175 °C. Sublimation (150 °C/1 P_a) yielded white plates, m.p. 174-175 °C. [Found: C 45.5 ; H 2.87; Cl 19.4 ; N 15.0 . Calc. for C₇H₅ClN₂S (184.65): C 45.53; H 2.73; Cl 19.20; N 15.17.] ¹H NMR (60 MHz, acetone-d₆): δ 7.88 (H3 and H5, s, 2H), 7.55 (H1, s broad, 1H), 7.02 (H3' or H4', d, 1H), 6.95 (H3' or H4', d, 1H). J (H3', H4') 4.2 Hz. m/e (%): 186, 184 (37, 100, M⁺), 159, 157 (4, 11, M⁺-HCN), 149 (20, M⁺-Cl), 132, 130 (11, 29, M-2HCN), 122 (17, M⁺-Cl, HCN), 105 (18, M⁺-ClCS).

4-(2'-Thienyl)pyrazole (1a) via dechlorination of 4-(5'-chloro-2'-thienyl)pyrazole (6). Compound 6 (1.85 g, 10.0 mmol) was dissolved in dry tetrahydrofuran (40 ml) under nitrogen in a septum-sealed flask. The stirred solution was cooled to 0°C and butyllithium (22 ml of a 1.50 M solution in hexane, 33.0 mmol) was added dropwise during 10 min. The solution was kept at 0°C for 1 h. and was then poured onto ice (25 g). After neutralization with some acetic acid the organic solvents were evaporated. The remaining aqueous phase was filtered and the precipitate was recrystallized from 2-propanol, giving 1.09 g (73 %) of 1a as white plates, m.p. 163-164°C.

4-(2'-Thienyl)pyrazole (1a) from 2-(2'-thienyl)-3-aminopropenal. Hydrazine hydrate (6.0 g, 0.12 mol) was added to a solution of the hydrogenation product (18.1 g) of 2-thiophenemalonaldheydonitrile [9] in 96 % ethanol (100 ml) and the mixture was refluxed for 2 h. Evaporation of the solvent gave a semi-solid residue, which was dissolved in chloroform (300 ml). The resulting solution was filtered, washed with water and extracted with 8 M aq. HCl (4 x 75 ml). The combined acidic phases were washed (CHCl₃), treated with charcoal and neutralized to pH ≈ 7 with 2.5 M aq. NaOH. After cooling, the resulting precipitate was filtered off yielding 9.2 g of yellowish crystals, m.p. 160-163°C. Sublimation gave 7.45 g (38 %, based on thienylmalonaldheydonitrile) of 1a as white crystals, m.p. 163-164°C.

1-Methyl-4-(2'-thienyl)pyrazole (1b) from 1a. Sodium hydride (960 mg of a 55-60 % suspension in mineral oil, 22-24 mmol) was washed three times with pentane and covered with dry tetrahydrofuran (100 ml). To the stirred suspension 4-(2'-thienyl)pyrazole (3.00 g, 20.0 mmol) was added in portions. When the evolution of hydrogen was over,

methyl iodide (2.98 g, 21 mmol, 1.31 ml) was added and the flask was stoppered and kept in the dark overnight. After evaporation of the solvent, the residual white solid was taken up in water and dichloromethane. The organic layer was separated and the aqueous phase extracted with dichloromethane. The combined organic layers were washed (H_2O), dried ($MgSO_4$), filtered through neutral alumina and evaporated, which gave 3.07 g of white crystals, m.p. 63-64°C. Recrystallization from hexane yielded 2.93 g (89 %) of 1b as white plates, m.p. 64-65°C.

4-(3'-Thienyl)pyrazole (2a) was prepared in 40 % yield (based on thienyl-3-malonaldehydinitrile) from the hydrogenation product of thienyl-3-malonaldehydinitrile by the same procedure as 1a, and was after sublimation (160°C/25 Pa) obtained as white crystals, m.p. 216-217°C (closed capillary). [Found: C 56.0; H 4.07; N 18.5; S 21.0. Calc. for $C_7H_6N_2S$ (150.2): C 55.97; H 4.03; N 18.65; S 21.35.] 1H NMR (60 MHz, acetone- d_6): δ 7.90 (H3 and H5, s, 2H), 7.27-7.47 (H2', H4' and H5', m, 3H). m/e (%): 150 (100, M^+), 149 (6), 123 (13, $M-HCN$), 122 (10), 105 (20, M^+-CHS), 96 (36, M^+-2HCN).

1-Methyl-4-(3'-thienyl)pyrazole (2b) was prepared in 94 % yield from 2a by the same procedure as 1b and was obtained as white plates (hexane), m.p. 123-124°C. [Found: C 58.6; H 5.00; N 16.9; S 19.7. Calc. for $C_8H_8N_2S$ (164.2): C 58.50; H 4.91; N 17.06; S 19.53.] 1H NMR (100 MHz, $CDCl_3$): δ 7.67 (H3 or H5, s, 1H), 7.49 (H3 or H5, s, 1H), 7.35-7.13 (H2', H4' and H5', m, 3H), 3.88 (CH_3 , s, 3H). m/e (%): 164 (100, M^+), 163 (10), 149 (4), 137 (7), 136 (11), 123 (12), 122 (24), 119 (16).

1,2-Dimethyl-4-(2'-thienyl)pyrazolium perchlorate (1c).

1-Methyl-4-(2'-thienyl)pyrazole (1b) (492 mg, 3.00 mmol) was dissolved in 10 ml of tetrahydrofuran. Dimethyl sulfate (0.50 g, 4.0 mmol, 0.38 ml) was added and the solution was refluxed for 8 h. After cooling, conc. aq. ammonia (3 ml) was added and the mixture was left overnight. After evaporation of the solvents, the residue was dissolved in a minimum amount of water. The resulting solution was washed twice with ether and was then treated with 10 % perchloric acid (2 ml). The mixture was kept at 0-5°C for some hours, whereafter filtration yielded 0.52 g (62 %) of the title compound as white needles, m.p. 183-184°C.

[Found: C 38.7 ; H 4.24; N 9.95; Cl 12.6. Calc. for $C_9H_{11}ClN_2O_4S$ (278.7): C 38.78; H 3.98; N 10.05; Cl 12.72.] NMR (DMSO- d_6 , 100 MHz): δ 8.87 (H3 and H5, s, 2H), 7.62 (H5', dd, 1H), 7.42 (H4', dd, 1H), 7.19 (H3', dd, 1H), 4.15 (CH_3 , s, 6H). J (H3',H4') 3.6 Hz, J (H3',H5') 1.4 Hz, J (H4',H5') 5.4 Hz.

1,2-Dimethyl-4-(5'-thienyl)pyrazolium perchlorate (2c) was prepared from 2b in analogy with the preceding experiment and was obtained in 71 % yield as white needles, m.p. 185-187°C. [Found: C 38.7 ; H 4.08 ; N 9.93 ; Cl 12.6 . Calc. for $C_9H_{11}ClN_2O_4S$ (278.7): C 38.78; H 3.98; N 10.05; Cl 12.72.] NMR (DMSO- d_6 , 100 MHz): δ 8.87 (H3 and H5, s, 2H), 7.86 (H2', dd, 1H), 7.72 (H5', dd, 1H), 7.45 (H4', dd, 1H), 4.14 (CH_3 , s, 6H). J (H2',H4') 1.4 Hz, J (H2',H5') 3.0 Hz, J (H4',H5') 5.0 Hz.

Reactions of 1a, 1b, 2a, 2b and 1-(2'-thienyl)pyrazole [1] with sulfuric acid. The appropriate substrate (1.0 mmol) was added with stirring to 98 % sulfuric acid (3.0 ml) at 0°C. The mixture was stirred at this temperature for 20 min. and was then poured onto ice (15 g). After neutralization ($NaHCO_3$) the clear, colourless solution (mixture) was extracted with dichloromethane. The combined organic layers were washed (H_2O) and

dried (MgSO_4). Evaporation of the solvent yielded starting material
(checked by IR and TLC) in the following yield: 7 % (1a), 5 % (1b),
10 % (2a), 7 % (2b) and 50 % (1-(2'-thienyl)pyrazole).

Nitration of 1-methyl-4-(2'-thienyl)pyrazole (1b) with nitric acid in trifluoroacetic acid. To a stirred solution of 1b (328 mg, 2.00 mmol) in trifluoroacetic acid (7 ml) at 0 °C, 100 % nitric acid (90 μ l, 2.2 mmol) was added. The solution was kept at 0 °C for 15 min and was then poured onto ice-water. The water phase was neutralized (NaHCO_3) and extracted with dichloromethane. The combined organic phases were washed (H_2O), dried (MgSO_4) and filtered through silica gel which was subsequently washed with dichloromethane. Evaporation of the combined filtrates gave 336 mg (80 %) of a yellow crystalline mass, m.p. 140-145 °C. Column chromatography (silica gel/ ether) gave partial separation of two compounds. The less polar one was 1-methyl-4-(3'-nitro-2'-thienyl)pyrazole (8) obtained as yellow needles (MeOH), m.p. 85-86 °C. [Found: C 45.9; H 3.53; N 20.1. Calc. for $\text{C}_8\text{H}_7\text{N}_3\text{O}_2\text{S}$ (209.2): C 45.92; H 3.37; N 20.08.] NMR (100 MHz, CDCl_3): δ 8.06 (H3 or H5, s broad, 1H), 7.82 (H3 or H5, s broad, 1H), 7.60 (H4' or H5', d, 1H), 7.09 (H4' or H5', d, 1H), 3.96 ($-\text{CH}_3$, s, 3H). J (H4', H5') 5.9 Hz. m/e (%): 209 (79, M^+), 193 (5, M^+-O), 179 (9, M^+-NO), 166 (17), 163 (5, M^+-NO_2), 138 (14), 119 (100, $\text{M}^+-\text{CNO}_2\text{S}$).

The more polar compound was 1-methyl-4-(5'-nitro-2'-thienyl)pyrazole (10) obtained as yellowish green plates (MeOH), m.p. 159-160 °C. [Found: C 45.8; H 3.49; N 20.3. Calc. for $\text{C}_8\text{H}_7\text{N}_3\text{O}_2\text{S}$ (209.2): C 45.92; H 3.37; N 20.08.] NMR (100 MHz, CDCl_3): δ 7.89 (H4', d, 1H), 7.83 (H3 or H5, s broad, 1H), 7.77 (H3 or H5, s broad, 1H), 7.05 (H3', d, 1H), 3.97 (CH_3 , s, 3H). J (H3', H4') 4.4 Hz. m/e (%): 209 (83, M^+), 193 (3), 179 (17), 163 (11), 151 (11, $\text{M}^+-\text{NO}-\text{CO}$), 119 (100). GLC (NPGS, 2 m, 230°) of the crude product showed it to consist of 8 and 10 in the ratio 32:68.

Nitration of 1b with nitric acid in sulfuric acid.

a) 2 eq. of nitric acid: Pulverized 1b (164 mg, 1.00 mmol) was added to a stirred solution of 100 % nitric acid (87 μ l, 2.1 mmol) in sulfuric acid (3 ml) at 0 °C. After 20 min. at 0 °C, work-up as in the preceding experiment gave 222 mg (87 %) of a crystalline mass, m.p. 148-150 °C. Recrystallization from methanol afforded

1-methyl-4-(3',5'-dinitro-2'-thienyl)pyrazole (11) as brownish yellow needles, m.p. 149-150 °C. [Found: C 38.0; H 2.78; N 22.0.

Calc. for $C_8H_6N_4O_4S$ (254.2): C 37.79; H 2.38; N 22.04.]

NMR (60 MHz, $CDCl_3$): δ 8.38 (H4', s, 1H), 8.22 (H3 or H5, s broad, 1H), 7.92 (H3 or H5, s broad, 1H), 4.03 (CH_3 , s, 3H). m/e (%):

254 (100, M^+), 238 (7, M^+-O), 224 (8, M^+-NO), 211 (16), 208, (14, M^+-NO_2), 196 (7, $M^+-NO-CO$), 167 (91).

b) 1 eq. of nitric acid: The same procedure as above, but using 42 μ l (1.0 mmol) of nitric acid yielded 124 mg of a crystalline mass, m.p. 129-133 °C. GLC (NPGS, 2 m, 230 °)/MS gave four peaks with retention times 13, 19, 24 and 66 min., corresponding to (comparison with authentic samples and their MS) 8, unknown (9) MS see below, 10 and 11.

From the GLC the proportions between 8, 9 and 10 were determined to 13:2:85 (quantitative analysis of 11 by GLC was not reproducible).

From the NMR spectrum ($CDCl_3$) of the crude product, the ratio between 11 and mononitro isomers was determined to 7:3. MS of 9; m/e (%):

209 (70, M^+), 193 (20), 179 (20), 163 (9), 149 (100), 119 (97).

c) 0.5 eq. of nitric acid: Pulverized 1b (164 mg, 1.00 mmol) was added with stirring to sulfuric acid at 0 °C. When all substrate had dissolved (about 2 min), a cold solution of 100 % nitric acid (21 μ l, 9.5 mmol) in sulfuric acid (0.5 ml) was added dropwise. After 20 min. at 0 °C the reaction mixture was kept for 20 min. at room temperature before work-up. Analysis as under b) gave the result given in the table (entry 3).

Nitration of 1b with acetyl nitrate. 100 % nitric acid (84 μ l, 2.0 mmol) was mixed with acetic anhydride (1 ml) at 0 $^{\circ}$ C. The mixture was kept at room temperature for 15 min., cooled to 0 $^{\circ}$ C and then slowly added to a solution of 1b (164 mg, 1.00 mmol) in 6 ml of acetic anhydride at 0 $^{\circ}$ C. After 1 h. at 0 $^{\circ}$ C, the reaction mixture was poured onto dilute aq. Na_2CO_3 . The resulting mixture was extracted with dichloromethane. The combined extracts were washed (H_2O) and dried (MgSO_4). The solution was concentrated and was then filtered through neutral aluminium oxide, which was subsequently washed with dichloromethane. The combined filtrates were evaporated, which gave 148 mg (71 %) of a yellow crystalline mass, m.p. 135-143 $^{\circ}$ C. GLC (NPGS, 230 $^{\circ}$)/MS gave three peaks with retention times 5, 14 and 26 min. corresponding to unknown (12) MS see below, 8 and 10 in the proportions 1:39:60. MS of 12; m/e (%): 209 (M^+ , 100), 192 (7, $\text{M}^+ - \text{OH}$), 179 (10), 136 (27), 119 (3), 95 (52).

Nitration of 2b with nitric acid in trifluoroacetic acid. The same scale and procedure as in the corresponding nitration of 1b was used. However, after 15 min. at 0 $^{\circ}$ C, most of the starting material remained (GLC, NPGS) and the reaction mixture was kept for a further 45 min. at 0 $^{\circ}$ C and 1 h. at 25 $^{\circ}$ C before work-up. This yielded 355 mg (85 %) of yellow crystals, m.p. 85-90 $^{\circ}$ C. One recrystallization from methanol afforded pure 1-methyl-4-(2'-nitro-3'-thienyl)pyrazole (14) as yellow crystals, m.p. 93-94 $^{\circ}$ C. [Found: C 45.8 ; H 3.29; N 19.9. Calc. for $\text{C}_8\text{H}_7\text{N}_3\text{O}_2\text{S}$ (209.2): C 45.92; H 3.37; N 20.08.] NMR (60 MHz, CDCl_3): δ 8.25 (H3 or H5, s, 1H), 7.92 (H3 or H5, s, 1H), 7.50 (H4' or H5', d, 1H), 7.22 (H4' or H5', d, 1H), 4.00 (CH_3 , s, 3H). J (H4', H5') 5.8 Hz. m/e (%): 209 (100, M^+), 193 (3), 179 (5), 166 (30), 151 (11), 119 (100).

The mother liquor was concentrated and impure 14 was filtered off. The residue from evaporation of the filtrate was chromatographed on a silica column with ether, which first gave 14 and then a new compound contaminated with 14 (TLC: silica, ether). Recrystallization of the latter fraction from carbon tetrachloride gave pure 1-methyl-4-(5'-nitro-3'-thienyl)pyrazole (16) as lemon yellow plates, m.p. 143-144 °C. [Found: C 45.7 ; H 3.42; N 19.8 . Calc. for $C_8H_7N_3O_2S$ (209.2): C 45.92; H 3.37; N 20.08.] NMR (60 MHz, $CDCl_3$): δ 7.99 (H4' or H2', d, 1H), 7.70 (H3 or H5, s, 1H), 7.63 (H3 or H5, s, 1H), 7.42 (H4' or H2', d, 1H), 3.97 (CH_3 , s, 3H). J (H2', H4') 1.7 Hz. m/e (%): 209 (100, M^+), 193 (2), 179 (2), 163 (14), 119 (64). GLC (NPGS, 230°)/MS of the crude product gave 3 peaks with retention times 17, 22, and 27 min., corresponding to the unknown 15 (MS see below), 14 and 16 in the proportions 1:90:9. m/e (%): 209 (100, M^+), 193 (4), 179 (11), 166 (26), 149 (56), 119 (17).

Nitration of 2b with nitric acid in sulfuric acid.

a) 2 eq. of nitric acid: The same scale and procedure as in the corresponding nitration of 1b was used, but with a reaction time of 45 min. This yielded 214 mg (82 %) of an orange-yellow crystalline mass, m.p. 150-155 °C. Column chromatography (silica/ether) gave two fractions. The less polar one consisted of 1-methyl-4-(2',4'-dinitro-3'-thienyl)pyrazole (17), obtained as lemon yellow needles (MeOH), m.p. 177-178 °C. [Found: C 37.8 ; H 2.72; N 21.5 . Calc. for $C_8H_6N_4O_4S$ (254.2): C 37.79; H 2.38; N 22.04.] 1H NMR (100 MHz, $DMSO-d_6$): δ 8.98 (H5', s, 1H), 8.00 (H3 or H5, s broad, 1H), 7.61 (H3 or H5, s broad, 1H), 3.89 (CH_3 , s, 3H). ^{13}C NMR ($DMSO-d_6$): δ 140.6 (C5'). J (C5', H5') 199.0 Hz. m/e (%): 254 (100, M^+), 238 (5, M^+-O), 225 (19), 224 (7, M^+-NO), 196 ($M^+-NO-CO$), 180 (30).

The more polar fraction consisted of 1-methyl-4-(2',5'-dinitro-3'-thienyl)pyrazole (18), obtained as orange-yellow plates (MeOH), m.p. 179-180°C. [Found: C 37.8 ; H 2.64 ; N 21.6 . Calc. for $C_8H_6N_4O_4$ (254.2): C 37.79; H 2.38; N 22.04.] 1H NMR (100 MHz, DMSO- d_6): δ 8.59 (H3 or H5, s broad, 1H), 8.56 (H4', s, 1H), 8.20 (H3 or H5, s broad, 1H), 3.92 (CH₃, s, 3H). ^{13}C NMR (DMSO- d_6): δ 129.8 (C4'). J (C4', H4') 181.9 Hz. m/e (%): 254 (100, M^+), 224 (2, M^+-NO), 211 (13), 208 (6, M^+-NO_2), 196 (8, $M^+-NO-CO$), 168 (38).

Integration of the 1H NMR spectrum of the crude product gave the ratio 17 to 18 as 39:61.

b) 1 eq. of nitric acid: The same procedure as above, but using 42 μ l (1.0 mmol) of nitric acid yielded 120 mg of crystals, m.p. 125-135°C.

TLC (silica, ether) gave four spots, indicating 14, 16, 17 and 18.

This was confirmed by the NMR (100 MHz, DMSO- d_6) spectrum of the crude product and integration gave the proportions of 14:16:17:18 as 34:8:14:44.

GLC (NPGS, 230°C, retains dinitro isomers 17 and 18) / MS gave the ratio 14 to 16 as 82:18 and showed also that 15 was formed in trace amounts.

c) 0.5 eq. of nitric acid: The same procedure as in the corresponding experiment of 1b was used. Results are given in the table (entry 9).

Nitration of 1-methyl-4-(2'-nitro-3'-thienyl)pyrazole (14) (93 mg, 0.44 mmol) by the procedure under b) yielded 102 mg (91 %) of yellow crystals, m.p. 160-170°C. TLC (silica, ether) gave two spots, corresponding to 17 and 18. Integration of the NMR (100 MHz, DMSO- d_6) gave the ratio 17 to 18 as 79:21.

Nitration of 2b with acetyl nitrate. The same procedure as in the corresponding nitration of 1b was used but the reaction time was 20 h. (after 1 h. much of the starting material still remained (TLC, silica/ether)). Work-up gave 154 mg (74 %) of a yellow crystalline mass, m.p. 40-60°C. GLC (NPGS, 230°C)/MS gave two peaks (both $m/e = 209$) with retention times of 6.5 and 24 min. Column chromatography (silica, dichloromethane/ether, 1:1) afforded two fractions. The less polar one consisted of 1-methyl-3(or 5)-nitro-4-(3'-thienyl)pyrazole (19) obtained as a viscous yellow oil. [Found: C 45.7 ; H 3.18; N 20.1 . Calc. for $C_8H_7N_3O_2S$ (209.2): C 45.92; H 3.37; N 20.08.] NMR (100 MHz, $CDCl_3$): δ 7.62 (H3 or H5, s, 1H), 7.67-7.63 and 7.42-7.24 (H2', H4' and H5', m, 3H), 4.22 ($-CH_3$, s, 3H). m/e (%): 209 (68, M^+), 193 (5), 192 (5), 180 (12), 179 (13), 136 (17), 119 (8), 95 (100).

The more polar fraction contained 14 identified by GLC/MS and NMR. Integration of the NMR spectrum of the crude mixture gave the ratio 14:19 as 88:12.

Nitration of 1,2-dimethyl-4-(2'-thienyl)pyrazolium perchlorate (1c) in TFA. Compound 1c (56 mg, 0.2 mmol) was dissolved in TFA (0.6 ml). The solution was cooled to 0°C and 100 % nitric acid (10 μ l, 0.24 mmol) was added. The solution was kept at 25°C for 15 min., whereafter its NMR spectrum (addition of TMS) was recorded. No starting material could be detected but the 3'-nitro and 5'-nitro derivatives were found in the ratio 3:7.

1,2-Dimethyl-4-(3'-nitro-2'-thienyl)pyrazolium perchlorate (1c) (TFA, 60 MHz): δ 8.57 (H3 and H5, s, 2H), 7.86 (H4' or H5', d, 1H), 7.55 (H4' or H5', d, 1H), 4.36 (CH_3 , s, 6H). J (H4', H5') 5.6 Hz.

1,2-Dimethyl-4-(5'-nitro-2'-thienyl)pyrazolium perchlorate:

^1H NMR (TFA, 60 MHz): δ 8.53 (H3 and H5, s, 2H), 8.09 (H3' or H4', d, 1H), 7.40 (H3' or H4', d, 1H), 4.36 (CH_3 , s, 6H). $\underline{J}$ (H3', H4') 4.4 Hz.

Nitration of 1,2-dimethyl-4-(3'-thienyl)pyrazolium perchlorate (2c) in TFA was performed as the preceding experiment and gave the 2'-nitro and 5'-nitro derivatives in the ratio 7:3.

1,2-Dimethyl-4-(2'-nitro-3'-thienyl)pyrazolium perchlorate:

^1H NMR (TFA, 60 MHz): δ 8.60 (H3 and H5, s, 2H), 7.80 (H4' or H5', d, 1H), 7.30 (H4' or H5', d, 1H), 4.32 (CH_3 , s, 6H). $\underline{J}$ (H4', H5') 5.6 Hz.

1,2-Dimethyl-4-(5'-nitro-3'-thienyl)pyrazolium perchlorate:

^1H NMR (TFA, 60 MHz): δ 8.40 (H3 and H5, s, 2H), 8.23 (H2' or H4', d, 1H), 7.93 (H2' or H4', d, 1H), 4.28 (CH_3 , s, 6H). $\underline{J}$ (H2', H4') 1.8 Hz.

Bromination of 1b with NBS. A solution of N-bromosuccinimide (178 mg, 1.00 mmol) in acetic acid (5 ml) was added to a solution of 1b (164 mg, 1.00 mmol) in acetic acid (10 ml) at 25°C. After 1 min., all NBS was consumed (test with NaI) and the reaction mixture was poured into water. The water phase was neutralized (Na_2CO_3) to $\text{pH} \approx 7$ and extracted with dichloromethane. The combined extracts were washed (aq. NaOH, H_2O) and dried (MgSO_4). Evaporation of the solvent gave 231 mg (95 %) of 1-methyl-(5'-bromo-2'-thienyl)pyrazole (13) as a white, crystalline mass, m.p. 101-102°C. Recrystallization from hexane gave white plates, m.p. 102.0-102.5°C. [Found: C 39.7 ; H 3.15 ; N 11.5 ; Br 32.6 . Calc. for $\text{C}_8\text{H}_7\text{N}_2\text{SBr}$ (243.1): C 39.52; H 2.90; N 11.52; Br 32.87.] NMR (100 MHz, CDCl_3): δ 7.59 (H3 or H5, s, 1H), 7.46 (H3 or H5, s, 1H), 6.94 (H3' or H4', d, 1H), 6.78 (H3' or H4', d, 1H), 3.89 ($-\text{CH}_3$, s, 3H). $\underline{J}$ (H3', H4') 3.9 Hz. m/e (%): 244, 242 (100, 99, M^+), 163 (14, M^+-Br), 119 (45, $\text{M}^+-\text{Br}-\text{CS}$).

Bromination of 2b with NBS. The same procedure as above was used and 219 mg of a slowly crystallizing oil was obtained. Recrystallization from hexane afforded pure 1-methyl-4-(2'-bromo-3'-thienyl)pyrazole (20) as white plates, m.p. 47.5-48.0 °C. [Found: C 39.6; H 3.10; N 11.4 ; Br 33.1 . Calc. for $C_8H_7N_2SBr$ (243.1): C 39.52; H 2.90; N 11.52; Br 32.87.] NMR (100 MHz, $CDCl_3$): δ 7.85 (H3 or H5, s, 1H), 7.81 (H3 or H5, s, 1H), 7.55 (H4' or H5', d, 1H), 7.02 (H4' or H5', d, 1H) 3.93 (CH_3 , s, 3H). J (H4', H5') 5.8 Hz. m/e (%): 244, 242 (100, M^+), 202, 200 (11), 163 (13, M^+-Br), 136 (12), 119 (49, $M^+-Br-CS$). GLC (NPGS, 180°) of the crude product showed it - beside some starting material (< 1 %) - to consist of 20 and unknown 21 (MS see below) in the ratio 98:2. m/e (%): 244, 242 (100, M^+), 163 (18, M^+-Br), 119 (51, $M^+-Br-CS$).

Competitive bromination of 1b (58 mg, 0.35 mmol) and 1-(2-thienyl)-pyrazole (53 mg, 0.35 mmol) in acetic acid (3 ml) with NBS (13 mg, 0.07 mmol) in acetic acid (1 ml) was performed in analogy with the preceding brominations. Analysis of the product mixture (101 mg) was performed by GLC (NPGA, trimmer acid, Chromosorb W 3:0.75:96.25; 1.8 m , 160-200°C).

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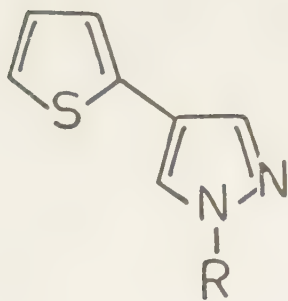
Table I. Some substitution reactions and their products

Entry	Reaction ^a	Composition of isolated material in mol %					Yield %
		<u>8</u>	<u>9</u>	<u>10</u>	<u>11</u>	<u>12</u>	
1	<u>1b</u> + HNO ₃ , TFA, 0°C, 15 min.	32		68			80
2	<u>1b</u> + HNO ₃ , H ₂ SO ₄ , 0°C, 20 min.	4	<1	25	70		52 (88 ^b)
3	<u>1b</u> + HNO ₃ , H ₂ SO ₄ , 0°C, 20 min.	20	<1	69	10		86 ^b
4	<u>1b</u> + HNO ₃ , H ₂ SO ₄ , 0°C, 20 min.				100		87
5	<u>1b</u> + AcONO ₂ , Ac ₂ O, 0°C, 1 h.	39		60		1	71
<u>13</u>							
6	<u>1b</u> + NBS, AcOH, 25°C, 1 min.	100					95
<u>14</u> <u>15</u> <u>16</u> <u>17</u> <u>18</u>							
7	<u>2b</u> + HNO ₃ , TFA, 0-25°C, 2 h.	90	1	9			85
8	<u>2b</u> + HNO ₃ , H ₂ SO ₄ , 0°C, 20 min.	34	<<1	8	14	44	52 (80 ^b)
9	<u>2b</u> + HNO ₃ , H ₂ SO ₄ , 0°C, 20 min.	47	5	48			83 ^b
10	<u>2b</u> + HNO ₃ , H ₂ SO ₄ , 0°C, 45 min.				39	61	82
11	<u>14</u> + HNO ₃ , H ₂ SO ₄ , 0°C, 45 min.				79	21	91
<u>14</u> <u>19</u>							
12	<u>2b</u> + AcONO ₂ , Ac ₂ O, 0°C, 20 h.	88	12				74
<u>20</u> <u>21</u>							
13	<u>2b</u> + NBS, AcOH, 25°C, 1 min.	98	2				89

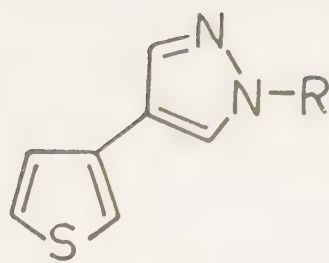
Cont'd Table I

^a Equimolar amounts of reagents were used, except in entries 3 and 9 (0.5 eq. HNO_3), 4 and 10 (2.0 eq. HNO_3) and in entries 5 and 2 (2.0 eq. AcONO_2).

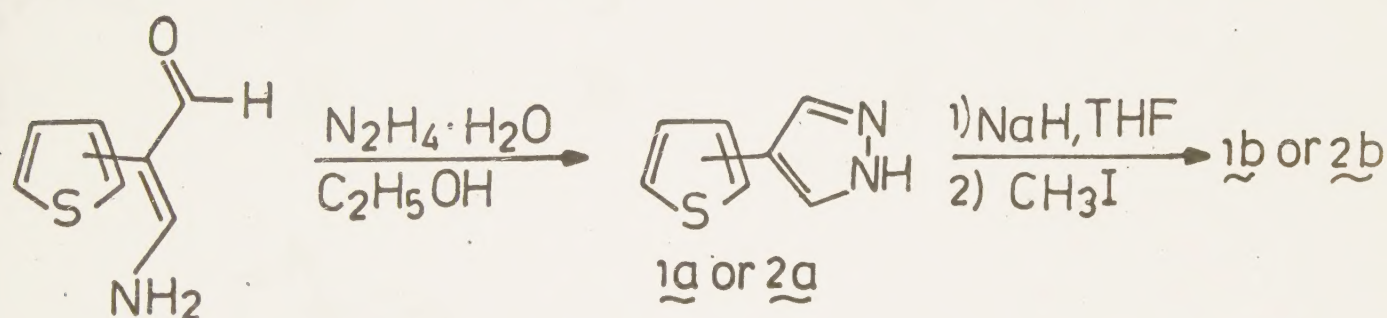
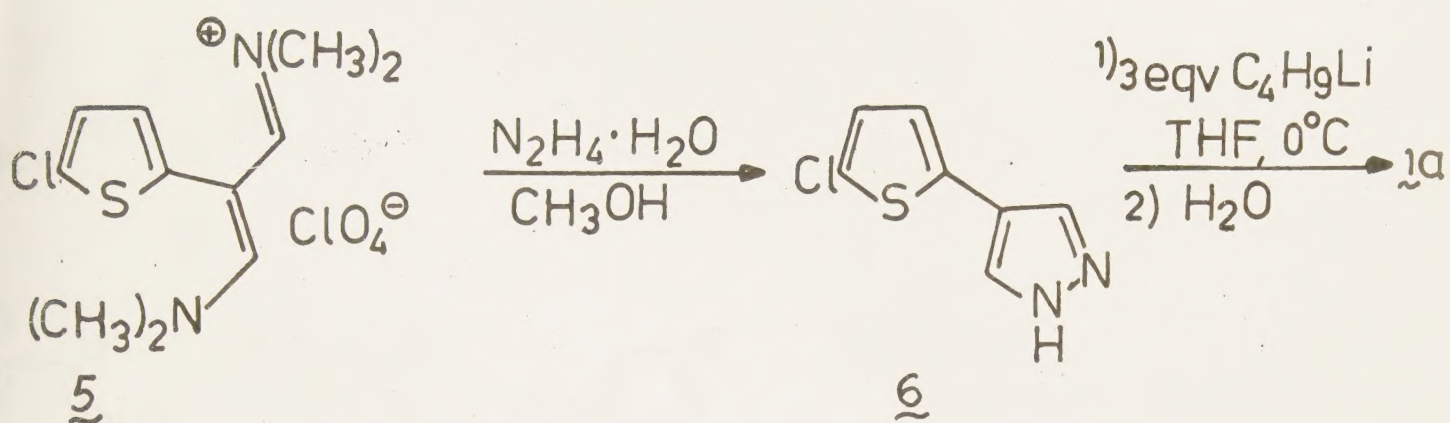
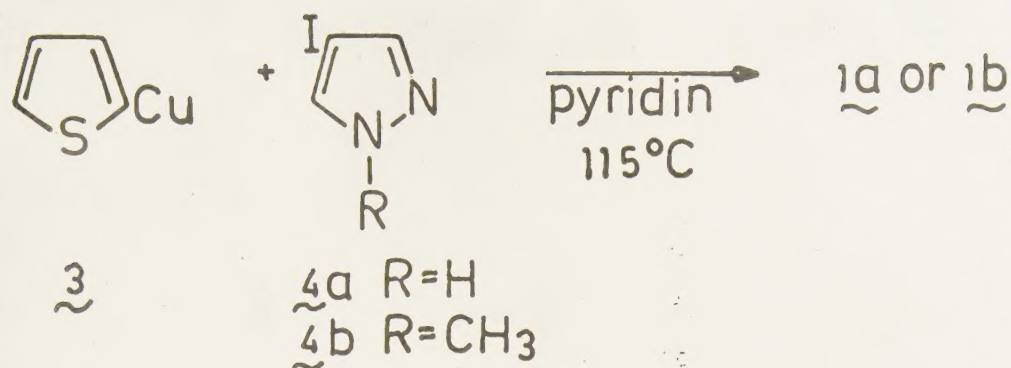
^b Yield based on nitric acid.



1a R=H
1b R=CH₃

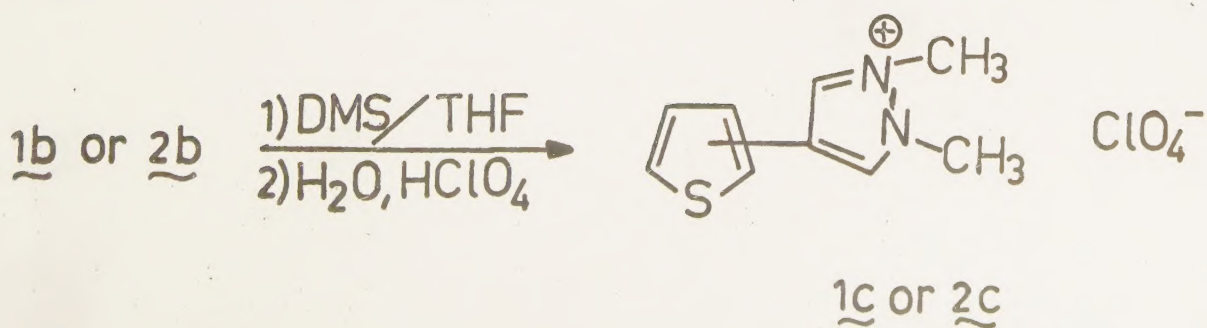


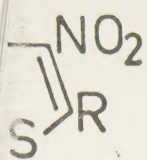
2a R=H
2b R=CH₃



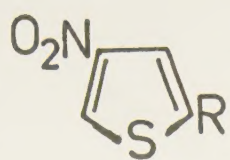
7a 2-thienyl
7b 3-thienyl

Scheme 1

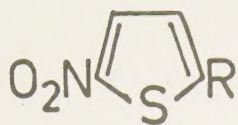




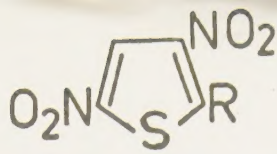
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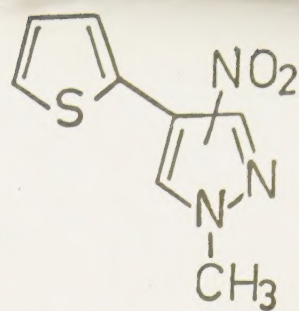
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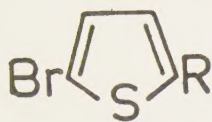
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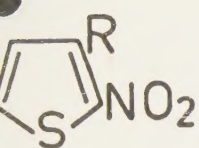
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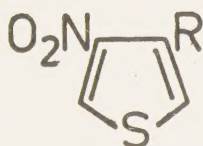
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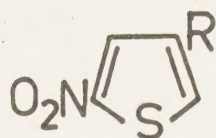
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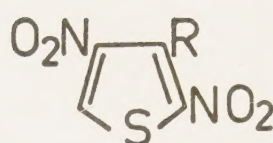
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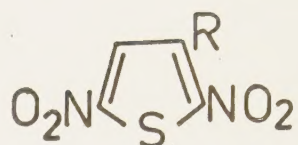
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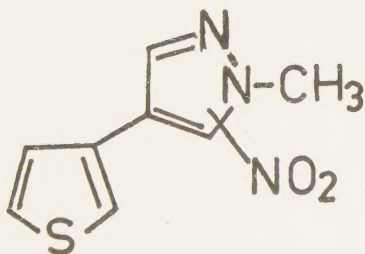
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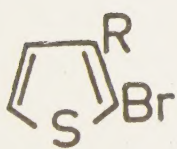
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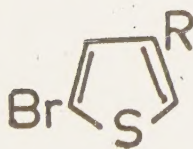
18



19



20



21

R=

